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Pylorus Preserving Pancreaticoduodenectomy Versus Standard Whipple Procedure

A Prospective, Randomized, Multicenter Analysis of 170 Patients With Pancreatic and Periampullary Tumors

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Objective: A prospective randomized multicenter study was performed to assess whether the results of pylorus-preserving pancreaticoduodenectomy (PPPD) equal those of the standard Whipple (SW) operation, especially with respect to duration of surgery, blood loss, hospital stay, delayed gastric emptying (DGE), and survival.

Summary Background Data: PPPD has been associated with a higher incidence of delayed gastric emptying, resulting in a prolonged period of postoperative nasogastric suctioning. Another criticism of the pylorus-preserving pancreaticoduodenectomy for patients with a malignancy is the radicalness of the resection. On the other hand, PPPD might be associated with a shorter operation time and less blood loss.

Methods: A prospective randomized multicenter study was performed in a nonselected series of 170 consecutive patients. All patients with suspicion of pancreatic or periampullary tumor were included and randomized for a SW or a PPPD resection. Data concerning patients' demographics, intraoperative and histologic findings, as well as postoperative mortality, morbidity, and follow-up up to 115 months after discharge, were analyzed.

Results: There were no significant differences noted in age, sex distribution, tumor localization, and staging. There were no differences in median blood loss and duration of operation between the 2 techniques. DGE was observed equally in the 2 groups. There was only a marginal difference in postoperative weight loss in favor of the standard Whipple procedure. Overall operative mortality was 5.3%. Tumor positive resection margins were found for 12 patients of the SW group and 19 patients of the PPPD group ($P < 0.23$). Long-term follow-up showed no significant statistical differences in survival between the 2 groups ($P < 0.90$).

Conclusions: The SW and PPPD operations were associated with comparable operation time, blood loss, hospital stay, mortality, morbidity, and incidence of DGE. The overall long-term and disease-free survival was comparable in both groups. Both surgical procedures are equally effective for the treatment of pancreatic and periampullary carcinoma.

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Pancreatic cancer is one of the most fatal malignant diseases today and ranks fifth in cancer mortality worldwide. Survival after surgery is still disappointing, with 5-year survival rates ranging from 10% to 29%.[1–6]

The introduction of partial pancreaticoduodenectomy is credited to Godivilla, an Italian surgeon, and Kausch,[7] a German surgeon from Berlin. Later on, this technique was refined by Whipple et al.[8]

Several modifications have been reported, including the pylorus-preserving pancreaticoduodenectomy (PPPD) described by Watson in 1944.[9]

This technique was reintroduced by Traverso and Longmire[10] in the late 1970s for chronic pancreatitis. Preservation of the pylorus in pancreaticoduodenectomy has been shown in retrospective studies to lead to a long-term improvement in gastrointestinal function, as indicated by more postoperative weight gain, fewer peptic ulcers, and less dumping. Furthermore, the pylorus preserving procedure simplifies the operation, thus leading to shorter operations and less intraoperative blood loss.[11] Initial studies reported a high incidence of complications, including delayed gastric emptying, ulcerative lesions of the anastomosis,[12,13] and concern about

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resection margins.[5,14] Nevertheless, similar survival rates have been described for both techniques.[2,15–18]

Only 2 relatively small studies have been performed to study PPPD prospectively. In a prospective randomized study of 31 patients by Lin and Lin,[17] no differences in operation time, blood loss, and blood transfusion were observed. Delayed gastric emptying was observed more frequently after PPPD than after the Whipple procedure, with marginal statistical significance ($P = 0.08$). Seiler et al[19] found shorter operation time, less blood loss, and fewer blood transfusions in the PPPD group of their series of 77 patients. No difference in operative mortality was found, but the SW group exhibited a higher morbidity rate.

In a large randomized trial in which the extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma was compared with a standard resection to preserve the pylorus,[20,21]similar mortality and some increased morbidity in the extended resection group were reported.

We conducted a prospective randomized multicenter study to evaluate whether PPPD has an advantage over the standard Whipple (SW) procedure.

METHODS

Study Design

The study protocol was approved by the ethics committee of each center. Informed consent was obtained according to the local rules prevailing at each participating institution.

The following hospitals in the Netherlands participated: Erasmus Medical Center Rotterdam; University Hospital Maastricht; Leiden University Medical Center; Ignatius Hospital, Breda; Reinier de Graaf Gasthuis, Delft; De Weezenlanden Hospital, Zwolle, and Medical Center Leeuwarden.

The design of this prospective multicenter trial consisted of a pretreatment evaluation and a randomized treatment with either a SW or a PPPD. The postoperative morbidity and mortality data were evaluated every 3 months up to 115 months of follow-up.

Preoperative Evaluation

Preoperative workup was standardized in all centers. A CT scan of the upper abdomen and a chest x-ray were requested. In most cases, an ERCP also was performed. Percutaneous transhepatic cholangiography, angiography, CT-angiography and MRI were optional.

Inclusion Criteria

We included 170 consecutive patients between January 1992 and December 2000 with suspected pancreatic or periampullary cancer that was assumed to be resectable according to preoperative diagnostic imaging (CT and/or MRI). Patients with a previous gastric resection were excluded.

Exclusion Criteria

Patients with distant metastasis or local unresectable tumors, as indicated by preoperative workup and intraoperative findings, were excluded. Patients with direct invasion of the pylorus or stomach, as well as patients with positive peripyloric lymph nodes, were excluded; all of the remaining patients were included in the analysis for efficacy. However, for analysis of survival, patients with lesions other than pancreatic or periampullary adenocarcinoma were excluded.

Blinding and Randomization

An equal number of blind envelopes with protocols for the SW and the PPPD resection was prepared. The envelopes were used sequentially as patients were enrolled in the study. Therefore, there was strict randomization in both arms. Randomization was carried out in the operation room: a sealed envelope was opened only after it was ascertained that both operation techniques were feasible in the patient concerned. Eighty-seven patients were randomized for PPPD (50 male: 37 female) with a median age of 64 years. Eighty-three patients were randomized for a Whipple resection (58 male: 25 female), with a median age of 62 years. Two patients in the PPPD group were converted to the SW resection during operation as the surgeon expected duodenal involvement; these 2 patients remained for analysis in the PPPD group.

Surgery

All patients were placed on a regimen of prophylactic antibiotics consisting of 2 g cefazolin (Cefacidal, Bristol-Meyers Squibb, Woerden, Holland) and 500 mg metronidazol (Flagyl, Aventis Pharma, Hoevelaken, Holland). In addition, octreotide (Sandostatin, Novartis Pharma, Arnhem, Holland) was administered to all patients preoperatively and continued postoperatively for 7 days at a dosage of 100 μg given subcutaneously 3 times a day.[22]

Surgical Procedure

The standard, pylorus-preserving resection involved division of the duodenum 2 cm distal to the pylorus with resection of all of the duodenum distal to the transection site, removal of the gallbladder and common bile duct (proximal to the level of the cystic duct junction), resection of the head, neck, and uncinate process of the pancreas (underneath the superior mesenteric vein, lateral from the mesenteric-portal vein axis, flush with the superior mesenteric artery) and removal of the periampullary tumor. For the standard resection, a distal gastrectomy varying from 20% to 40% was performed. Frozen section was performed routinely at the transection site of the pancreatic remnant in all patients. In case of macroscopically suspected other margins, a frozen section of this margin was also performed. An end-to-side invaginated pancreaticojejunostomy was performed. Further downstream, an end-to-side hepaticojejunostomy and side-to-

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side gastroenterostomy or an end-to-side pylorus-jejunostomy was made.

Postoperative Management

All patients were managed according to a standard postoperative pathway. All patients received histamine H2-receptor antagonists as prophylaxis against stress ulceration, and octreotide treatment was continued for 7 days. At the end of the operation, a drain was left in the area of the pancreaticojejunostomy and the hepaticojejunostomy. The drain was removed if the amylase concentration was less than 300 U/L (less than twice the serum concentration) and production was less than 50 mL per day or after postoperative day 10. Pancreatic fistula was defined as drainage of more than 50 mL amylase-rich fluid per day through the surgically placed drains on or after postoperative day 10 or pancreatic anastomotic disruption demonstrated radiographically.

A biliary fistula was diagnosed if there was persistent secretion of bilirubin-rich drainage fluid of more 50 mL per day or after the 10th postoperative day.

Postoperative bleeding was defined as the need for more than 2 units of red blood cells more than 24 hours after surgery or relaparotomy for bleeding.

The nasogastric tube was removed when the production has decreased to less than 200 mL per 24 hours.

Delayed gastric emptying was defined as gastric stasis requiring nasogastric intubation for 10 days or more or the inability to tolerate a regular diet on the14th postoperative day.[23]

Nineteen (10 SW and 9 PPPD) patients received postoperative chemoradiotherapy according to the EORTC study in which the Erasmus Medical Center Rotterdam paticipated.[24]

Pathologic Review

All pathology specimens were reviewed to determine the primary pathologic diagnosis and the extent of the disease. Tumor stage was determined according to the UICC classification system and the TNM system.[25] Resection margins of the specimen were stained and were considered positive if the neoplasm was present at the pancreatic neck, uncinate processus, common bile duct, duodenum/gastric resection area, mesenteric artery, and portal vein and the circumferential margin, which is defined as the dorsal resection margin (peripancreatic fat and fascia of Trietz) or beyond the anterior pancreatic parenchyma anteriorly (peripancreatic fat, mesenteric base of the transverse colon, or posterior peritoneum of the lesser sac). A periampullary tumor was defined as a tumor of the ampulla of Vater or periampullary duodenum and distal common bile duct.

Follow-up

Patient follow-up, obtained via office records from the outpatient clinic, was completed up to May 2002. Patient demographics, intraoperative factors, pathologic findings, and postoperative course were evaluated. Parameters such as blood loss, duration of operation, delayed gastric emptying, intraoperative and postoperative complications, hospital stay, hospital mortality, and weight loss were recorded at discharge. Follow-up evaluations were conducted every 3 months following discharge. When signs of recurrent disease occurred during the interval, a CT scan or MRI was performed.

Statistical Analysis

Data were expressed as median and range. The primary endpoints in this study were blood loss, operation time, and hospital stay. The secondary endpoints were delayed gastric emptying and survival. A power-analysis for these endpoints, based on data from a former study, had shown that at least 65 patients with pancreatic and periampullary adenocarcinomas had to be included in each group.[15] With this number of patients, it should be possible to demonstrate ($\alpha = 0.05$; $\beta = 0.05$) that blood loss and operation time will be less (30% and 20%, respectively) with pylorus-preserving pancreaticoduodenectomy as compared with the SW resection. This number of patients was also considered to be sufficient to demonstrate a reduction of hospital stay. Survival was calculated from the

TABLE 1. Patient Characteristics

Patient Characteristics*	SW (n = 83)	PPPD (n = 87)	*P* Value
Age (y)	62 (27–78)	64 (43–78)	0.269
Gender, male/female	50/37	58/25	0.112
Weight preoperative (kg)	70.6 (46–102)	70.0 (43–110)	0.717

SW, standard Whipple; PPPD, pylorus-preserving pancreaticoduodenectomy.
*Data given are number of patients or median (range).

TABLE 2. Postoperative Complications, Relaparotomy, and Mortality

Complications	SW (n = 83)	PDDD (n = 87)	*P* Value
Pancreatic fistula	12 (14%)	11 (13%)	
GE leakage	2 (1%)	0	
Bile leakage	0	2 (2%)	0.528
Postoperative bleeding	6 (7%)	6 (7%)	0.933
Intra-abdominal abscess	8 (10%)	9 (10%)	0.878
Other complications	23 (28%)	19 (22%)	0.375
Relaparotomy	16 (19%)	13 (15%)	0.479
Mortality*	6 (7%)	3 (3%)	0.270

SW, standard Whipple; PPPD, pylorus-preserving pancreaticoduodenectomy.
*Operative mortality within 30 d.

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TABLE 3. Postoperative Days of Nasogastric Intubation, Days Until Normal Diet, Incidence of Delayed Gastric Emptying, Postoperative Hospital Stay in Days, and Lapse in Body Weight

Outcome	SW	PPPD	*P* Value
Days of nasogastric intubation	5 (1–48) [83]	6 (1–57) [87]	0.835
Days until regular diet tolerated orally	10 (0–54) [83]	10 (0–58) [87]	0.574
Delayed gastric emptying*	18 (23%) [80]	19 (22%) [85]	0.800
Hospital stay, days	20 (11–138) [67]	18 (4–175) [74]	0.488
Body weight on discharge (kg)	67 (44–92) [67]	65 (41–98) [74]	0.789
Pre-illness body weight (kg)	75 (53–92) [75]	79 (50–120) [76]	0.571
Preoperative body weight (kg)	71 (46–102) [77]	70 (46–102) [81]	0.764

*Delayed gastric emptying is defined as nasogastric suction for 10 d or more, or diet on or before the 14th postoperative day. Data given are median (range) or number of patients. Data given in brackets indicate number of patients concerned, ie, excluding patients not analyzed

date of surgery using the Kaplan-Meier method and compared with the log-rank test. Percentages were compared between groups using Fisher exact test or the χ^2 test. Other data were compared using the Mann-Whitney *U* test. The level of significance was set at $P < 0.05$.

RESULTS

Demographics and preoperative characteristics of this study are listed in Table 1.

Follow-up Results

Based on the final histologic diagnosis, 29 patients with benign lesions (14 in the SW group and 15 in the PPPD group) and 7 with endocrine tumors (3 in the SW group and 4 in the PPPD group) were excluded from the survival analysis. For long-term follow-up a total of 134 patients with histologic proven pancreatic and periampullary adenocarcinoma were included and analyzed. Median follow-up was 18.5 months (range 1–115 months). The median intraoperative blood loss was 2.0 L (0.3–9.5 L) in the SW resection group and 2.0 L (0.4–21.0 L) in the PPPD group, with a *P* value of 0.70. The median operative time was 300 minutes (range 160–480 minutes.) in the SW group and 300 minutes (range 130–600 minutes) in the PPPD group ($P = 0.10$).

Number of units of packed red blood cells given during operation was equal in both groups, with a median of 2 in each group ($P = 0.70$).

During the postoperative course, there were no differences in specific procedure-related or general complications. Sixteen patients in the SW group underwent a relaparotomy versus 13 patients in the PPPD group ($P = 0.40$; Table 2).

Days of nasogastric intubation were similar in both groups, with a median of 5 days (range 1–48) in the SW group and 6 days (range 1–57) in the PPPD group ($P = 0.80$). There were also no significant differences in days until regular diet was tolerated.

The incidence of delayed gastric emptying was comparable in both groups, 18 patients in the SW group and 19 patients in the PPPD group ($P = 0.80$). We did find a significant correlation between DGE and intra-abdominal complication (postoperative bleeding, abscess and intra-abdominal leakage) ($P < 0.05$).

The median hospital stay was in both groups equal (19 days; $P = 0.50$). Postoperative weight loss was observed in both groups, with a median of 8 kg in the SW resection group and 13.5 kg in the PPPD group ($P = 0.70$; Table 3). These differences equalize during follow-up (Fig. 1).

Pancreatic adenocarcinoma was found in 43 patients in the SW group and in 47 patients in the PPPD group (Table 4). Twenty-three patients in the SW group and 21 patients in the PPPD group were diagnosed with a periampullary carcinoma. Tumor-positive lymph nodes were found in 38 patients in the Whipple group versus 37 patients in the PPPD group ($P =$

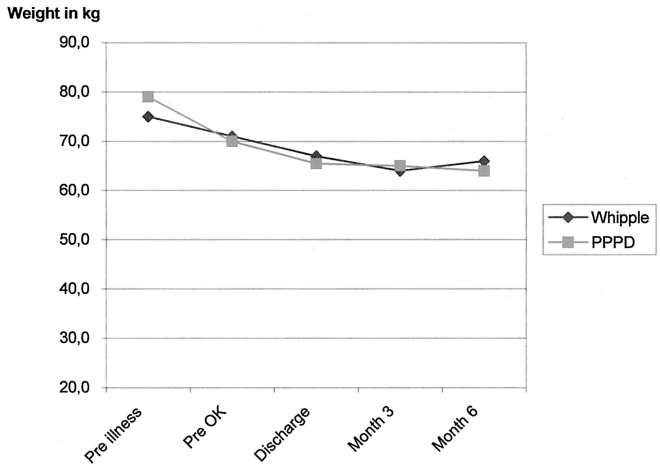

FIGURE 1. Body weight versus time of follow-up.

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TABLE 4. Pathology

Characteristics	SW (n = 83)	PDDD (n = 87)	*P* Value
Malignant			
Pancreatic adenocarcinoma	43 (52%)	47 (54%)	
Periampullary adenocarcinoma	23 (27%)	21 (24%)	
Other malignancy	3 (4%)	4 (5%)	
Total	69 (83%)	72 (83%)	
Benign			
Chronic pancreatitis	10 (12%)	9 (10%)	
Benign villous adenoma with dysplasia	4 (5%)	6 (7%)	
Total	14 (17%)	15 (17%)	
Lymph nodes	SW (n = 69)*	PDDD (n = 72)*	
Hepatoduodenal ligament	5 (7%)	4 (6%)	
Peripancreatic	26 (38%)	25 (35%)	
Mesenteric artery/vein	7 (10%)	6 (8%)	
Perigastric/pyloric	0	2 (2%)	
Tumor-negative lymph nodes	31 (45%)	35 (49%)	
	SW (n = 69)	PPPD (n = 72)	
Margins positive resection			
Duodenum/gastric	0	1 (1%)	
Pancreatic remnant	1 (1%)	1 (1%)	
V.porta/V.mesenterica	2 (3%)	2 (3%)	
Mesenteric artery	3 (4%)	4 (6%)	
Circumferential	5 (7%)	10 (14%)	
Inferior cava vein	1 (1%)	1 (1%)	
Total	12/69 (17%)	19/72 (26%)	0.230

SW, standard Whipple; PPPD; pylorus-preserving pancreaticoduodenectomy.
*Data given are number of patients. Peripancreatic: anterior and posterior pancreatoduodenal nodes. Circumferential margin: posterior resection margin and the margin beyond the pancreatic parenchyma anteriorly.

0.70). Locoregional tumor-positive lymph nodes were equally spread in both groups ($P = 0.60$).

Overall operative mortality rate was 5.3%; 6 patients in the SW group and 3 patients in the PPPD group died within 30 days.

The overall median disease-free survival was 14 months in the SW-group and 15 months in the PPPD group ($P = 0.80$). The overall disease-free survival was similar in both groups ($P = 0.90$). There was no difference in median overall survival rates between the 2 groups ($P = 0.90$; Fig. 2).

Periampullary cancer was diagnosed in 44 patients, of whom 21 patients underwent a PPPD and 23 patients a SW resection. The median disease-free survival was 49 months in the SW group and 23 months in the PPPD group ($P = 0.60$). Median survival in the SW group was 17 months versus 29 months in the PPPD group, which is not statistically significant ($P = 0.50$).

Ninety patients had pancreatic cancer, of whom 47 patients underwent a PPPD and 43 patients a SW. The median disease-free survival was 7 months in the SW group

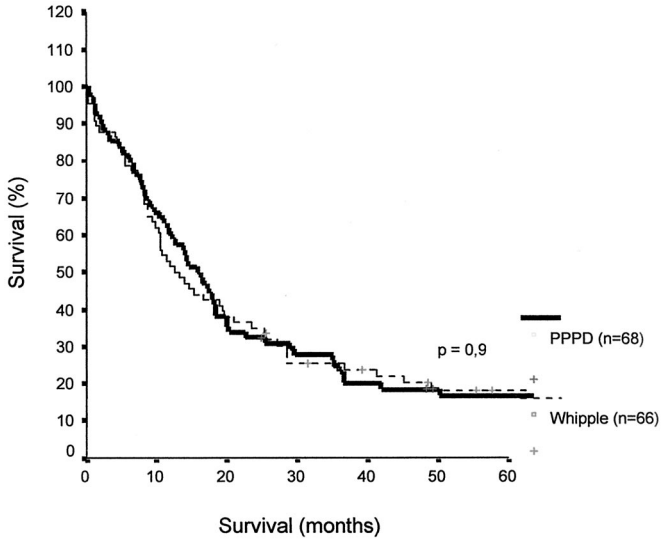

FIGURE 2. Overall survival rates for patients with adenocarcinoma.

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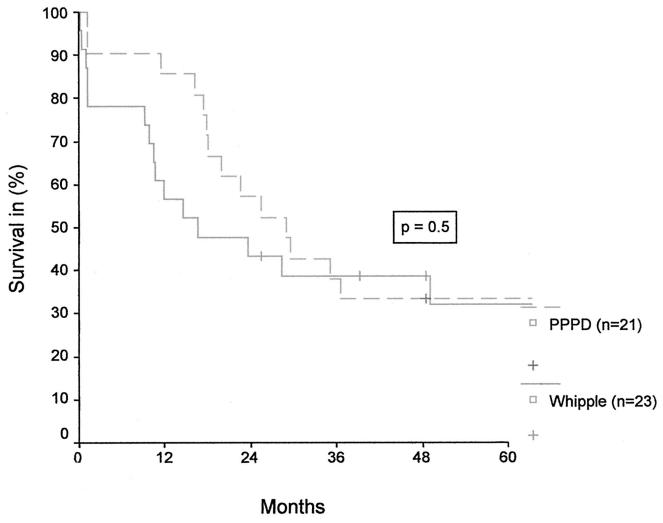

FIGURE 3. Periampullary adenocarcinomas (DBD, ampullary and duodenal carcinomas).

and 6 months in the PPPD group ($P = 0.90$) The median survival was 11 months in the SW group and 12 months in the PPPD group ($P = 0.70$).

Combining both carcinoma groups, there was no difference in median overall long-term survival rates between the 2 randomized groups as shown in Figure 3 ($P = 0.90$).

Tumor positive resection margins were noted in 12 (17%) patients in the SW group and 19 (26%) patients in the PPPD group ($P = 0.23$). Most of these positive margins were located at and around the pancreatic resection area, which was defined as circumferential (Table 4) and not on the pancreatic remnant (Fig. 4).

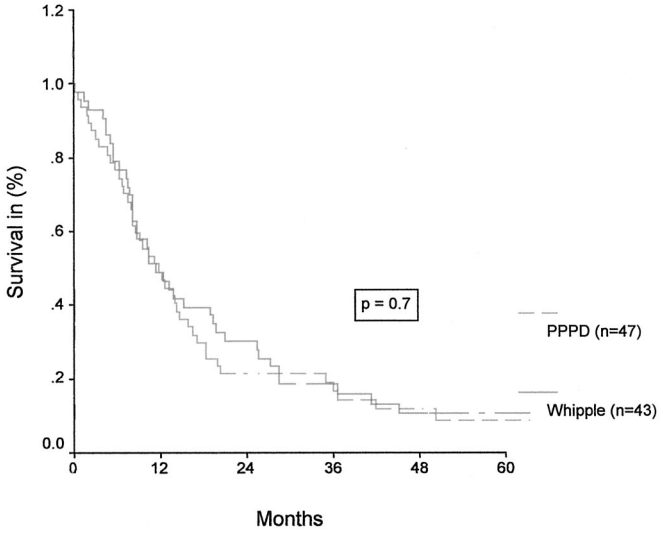

FIGURE 4. Pancreatic adenocarcinomas.

DISCUSSION

We hypothesized that PPPD is associated with a reduced operation time, less blood loss, shorter hospital stay, and a more physiological food passage. Two smaller randomized studies reported a shorter operation time and less blood loss, fewer transfusions, and a lower morbidity for the PPPD. However, the power of both studies might be considered low.[17,18]

In this study, the duration of the operation was equal for the 2 procedures. The median blood loss also did not differ between the 2 groups (2.0 L; Table 1). Compared with reports from some large centers,[20,26] blood loss in the present series was 2 times higher; however, in comparison to other multicenter studies[18,27] there are only small differences.

When the results of this study are analyzed, one must take into consideration the fact that we performed a multicenter analysis of both large-volume and small-volume centers, which is a realistic situation in most countries.

The overall operative mortality in this study was 5.3%. Multicenter studies are often associated with a higher mortality rate, ranging from 5% in Italy[27] to 10% in France[28] and 17.2% in the United States.[29]

PPPD has been associated with delayed gastric emptying, an increase in morbidity, and prolonged hospital stay. Warshaw and Torchiana[30] first reported this phenomenon after their initial study of 8 patients in 1978. According to the literature, the incidence of delayed gastric emptying is estimated to range between 25% and 70%,[12,15,23,30–36] which is sufficient reason for some to abstain from the PPPD procedure. The incidence of delayed gastric emptying in this study was equal in the 2 groups, 18 in the Whipple group versus 19 in the PPPD group.

Several factors are thought to play a role in the pathophysiology of delayed gastric emptying. In the present series, we found a correlation between delayed gastric emptying and intra-abdominal complications ($P < 0.05$). This relationship was reported previously.[23,37,38] Gastric dysrhythmias, disruption of gastroduodenal neural connections, ischemia of the pylorus muscle, and ligation of the right gastric artery all have been related to delayed gastric emptying.[32,39–42]Resection of the duodenum, the primary production site of most gastrointestinal hormones, might also play a role in the pathogenesis of this complication. Yeo et al[36] reported in a randomized trial that administration of erythromycin, a motulin agonist, decreased the incidence of DGE by 37%. Since this difference was not statistically significant, we did not include erythromycin as standard therapy.

In the present study, hospital stay, 20 days for the SW group and 18 days for the PPPD group, was not significantly different ($P = 0.50$). These results are comparable to other randomized studies.[18,27]

An argument in favor of pylorus preservation may be that patients subsequently have a better nutritional status

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compared with patients after a gastrectomy.[23,33] Postoperative weight loss was observed in both groups, with a median of 8 kg for the Whipple resection group versus 13.5 kg for the PPPD group. This is not statistically significant ($P = 0.70$). An argument against the use of PPPD for the resection of pancreatic tumors is the potential risk of positive duodenal resection margins,[5,14] resulting in lower survival rates. In this study, 1 patient in the PPPD group had a positive resection margin at the duodenal site. There were no significant differences in tumor positive resection margins; subsequently, we did not detect any significant differences in survival.

According to other randomized studies which compared the PPPD versus SW[18] and SW versus the extended pancreaticoduodenectomy,[27] our survival outcomes are highly comparable. It is important to note that we included the in-hospital mortality in our survival rate calculation in contrast to some other studies.[21] Furthermore, it should be noted that adjuvant therapy was not routinely provided in contrast to other trials.[21,43,44] We did not recommend adjuvant chemotherapy and radiotherapy for our patients since the outcome of the published trials comparing the effects of adjuvant chemoradiotherapy to surgery alone[24,45] did not show a statistically significant difference in survival in favor of the adjuvant therapy.

In conclusion, the incidence of delayed gastric emptying in this study of 170 consecutive patients was similar after PPPD and Whipple resection. Postoperative nasogastric drainage period was comparable in both groups. As far as the duration of operation, blood loss, hospital stay, and postoperative weight loss are concerned, there were also no significant differences. The PPPD appears to be just as radical compared with the SW procedure. Long-term survival and disease-free survival did not exhibit significant differences. Thus, both procedures are equally effective for treatment of pancreatic cancer.

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